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(54) 【発明の名称】 しわ形成予防剤

(57) 【要約】

【解決手段】 金属依存型エラスチン分解酵素阻害剤を有効成分とするしわ形成予防剤。

【効果】 皮膚の老化に伴うしわの形成を防止又は改善することができる。

## 【特許請求の範囲】

【請求項1】 金属依存型エラスチン分解酵素に対する阻害剤を有効成分とするしわ形成予防剤。

【請求項2】 金属依存型エラスチン分解酵素が、真皮線維芽細胞由来のエラスチン分解酵素である請求項1記載のしわ形成予防剤。

【請求項3】 投与形態が、皮膚外用剤である請求項1又は2記載のしわ形成予防剤。

【請求項4】 さらに、紫外線吸収剤又は紫外線防曇剤を含有するものである請求項1～3のいずれか1項記載のしわ形成予防剤。

## 【発明の詳細な説明】

## 【0001】

【発明に属する技術分野】本発明はしわ形成予防剤に関し、さらに詳細には皮膚の老化によって生じるしわの発生を防止又は改善することのできるしわ形成予防剤に関する。

## 【0002】

【従来の技術】皮膚が老化することにより生じる外観変化の代表例としては、しわ、たるみの発生、はりの減少、色素沈着、色調変化などがある。このうち、色素沈着については、研究が進み、各種の美白剤が開発され、市販されている。

【0003】ところで、しわの発生については、十分に研究が進んでいるとはいえないのが現状である。例えばコラーゲンを配合した化粧品が用いられているが、充分なしわ形成防止効果は得られていない。

【0004】しわの発生については、特に紫外線との関連性が強いとされており、紫外線照射により生じた皮膚の老化を光老化と称して、種々研究されている。しかし、まだ紫外線吸収剤又は紫外線防曇剤に代わる化粧品が開発されていないのが現状である。

## 【0005】

【発明が解決しようとする課題】従って、本発明の目的はしわの形成を予防又は改善することのできる薬剤又は化粧料を提供することにある。

## 【0006】

【課題を解決するための手段】そこで、本発明者らは、しわの形成とエラスチンとの関係に着目し、種々検討してきたところ、従来、皮膚の老化、特に光老化によって真皮のエラスチンは顕著に増加する（例えば、J. Invest. Dermatol., 82: 587-590(1984)、同91: 158-161(1988)、同103: 182-186(1994)）といわれていることから、エラスチンを減少させることがしわの防止につながると考えられてきた。一方、エラスチン分解酵素としては通常好中球由来のものが用いられており、該好中球由来のエラスチン分解酵素に対する阻害剤を用いた実験では、しわの形成に対する防止効果は全く認められなかった。そこで、さらに研究を続けた結果、エラスチン分解酵素にはセリンプロテアーゼに属するものと金属依存型プロ

テアーゼに属するものがあるが、そのうち、金属依存型のエラスチン分解酵素に対する阻害剤を投与した場合にのみしわの発生が有意に防止できることを見出し、本発明を完成するに至った。

【0007】すなわち、本発明は金属依存型エラスチン分解酵素に対する阻害剤を有効成分とするしわ形成予防剤を提供するものである。

## 【0008】

【発明の実施の形態】本発明に用いられる金属依存型エラスチン分解酵素阻害剤としては、金属依存型エラスターゼ阻害剤、特に真皮線維芽細胞由来の金属依存型エラスターゼ阻害剤が好ましい。このような阻害剤としては、例えば培養ヒト線維芽細胞から0.1%トリトンX-100/0.2M トリス-塩酸緩衝液(pH8.0)で抽出した酵素液を用い、N-サクシニル-Ala-Ala-p-ニトロアニリドを基質とした酵素活性測定系において1mMで50%以上の阻害活性を示す物質が挙げられる。

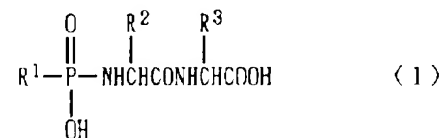
【0009】このような金属依存型エラスチン分解酵素阻害剤の例としては、例えばホスホン酸誘導体、メルカプトプロピオンアミド誘導体等が挙げられる。

【0010】ホスホン酸誘導体としては、次の一般式

(1)

【0011】

【化1】



【0012】(式中、R<sup>1</sup>、R<sup>2</sup>及びR<sup>3</sup>は水素原子、置換基を有していてもよい炭化水素基又は置換基を有していてもよい糖残基を示す)で表される化合物が挙げられる。

【0013】上記式(1)中、R<sup>1</sup>、R<sup>2</sup>及びR<sup>3</sup>で示される置換基を有していてもよい炭化水素基としては、飽和炭化水素基及び不飽和炭化水素基のいずれでもよく、アルキル基、アルケニル基、アルキニル基、環状アルキル基、環状アルケニル基、芳香族炭化水素基、アラールキル基等が挙げられる。これらの炭化水素基は、炭素数が1～24のもの、特に1～18のものが好ましい。

【0014】前記炭化水素基のうち、アルキル基、環状アルキル基、芳香族炭化水素基又はアラールキル基が好ましい。ここで、アルキル基としては直鎖状又は分枝状の炭素数1～12のアルキル基が好ましく、例えば、メチル基、エチル基、n-プロピル基、イソプロピル基、n-ブチル基、イソブチル基、sec-ブチル基、tert-ブチル基、n-ペンチル基、イソアミル基、tert-アミル基、n-ヘキシル基、n-オクチル基、n-

デシル基、n-ドデシル基などが挙げられる。環状アルキル基としては5～7員環の脂環状アルキル基が好ましく、シクロペンチル基、シクロヘキシル基、シクロヘプチル基等が挙げられる。芳香族炭化水素基としては、フェニル基、ナフチル基等の炭素数6～14の芳香族炭化水素基が好ましい。アラルキル基としては炭素数6～12の芳香族炭化水素基で置換された炭素数1～5のアルキル基が好ましく、例えば、フェニルメチル(=ベンジル)基、2-フェニルエチル(=フェネチル)基、1-ナフチルメチル基、2-ナフチルメチル基、2-(1-ナフチル)エチル基、2-(2-ナフチル)エチル基、3-フェニルプロピル基などが挙げられる。

【0015】また、これらの炭化水素基に置換し得る基としては、ハロゲン原子、ヒドロキシル基、アルコキシ基、アシル基、保護されていてもよいアミノ基、複素環式基等が挙げられる。ここでハロゲン原子としては塩素原子、臭素原子、ヨウ素原子等が挙げられる。アルコキシ基としては、炭素数1～12のアルコキシ基が好ましく、例えばメトキシ基、エトキシ基、イソプロポキシ基等が挙げられる。アシル基としては、炭素数1～12のアルカノイル基が好ましく、例えばアセチル基、プロピオニル基、ブチリル基等が挙げられる。保護されていてもよいアミノ基としては、アミノ基、アシルアミノ基、アルキルアミノ基、ジアルキルアミノ基等が挙げられる。複素環式基としては、ヘテロ原子として窒素原子、酸素原子及び/又は硫黄原子を1～3個有する5～11員の単環又は縮合環の基が好ましく、例えばピリジル基、ピリダジニル基、フリル基、チエニル基、インドリル基、チアゾリル基、イミダゾリル基、ベンゾフリル基、ベンゾチエニル基等が挙げられる。

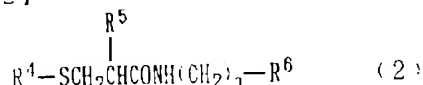
【0016】糖残基としては、単糖残基又はオリ糖残基が挙げられる。またこれらの糖残基に置換し得る基としては、アルキル基、アシル基、アラルキル基等が挙げられる。ここでアルキル基、アシル基、アラルキル基としては前記と同様のものが挙げられる。

【0017】これらのホスホン酸誘導体は、例えば特開平5-105698号公報に記載の方法によって製造することができる。

【0018】メルカプトプロピオンアミド誘導体としては、例えば次の一般式(2)

【0019】

【化3】



【0020】(式中、 $R^4$  は水素原子又はアシル基を示し、 $R^5$  は水素原子又は置換基を有していてもよい炭化水素基を示し、 $R^6$  は水素原子、カルボキシ基、アルコキシカルボニル基、置換基を有していてもよい炭化水素基、置換基を有していてもよい複素環式基又はアシル

基を示し、 $n$ は1～20の数を示す)で表される化合物が挙げられる。

【0021】上記式(2)中、 $R^4$  及び $R^6$  で示されるアシル基としては、アルカノイル基及びアリールカルボニル基が挙げられる。当該アルカノイル基としては炭素数1～12のアルカノイル基が好ましく、例えばアセチル基、プロピオニル基、ブチリル基等が挙げられる。またアリールカルボニル基としては、炭素数7～15のアリールカルボニル基が好ましく、例えばベンゾイル基、置換ベンゾイル基、ナフチルカルボニル基、置換ナフチルカルボニル基等が挙げられる。ここでベンゾイル基やナフチルカルボニル基に置換する基としてはアルキル基、アルコキシ基、ハロゲン基、アミノ基、ヒドロキシ基、アルカノイルオキシ基等が挙げられる。

【0022】 $R^5$  及び $R^6$  で示される置換基を有していてもよい炭化水素基としては、前記 $R^1$ 、 $R^2$  及び $R^3$  と同様のものが挙げられる。

【0023】 $R^6$  で示される複素環式基としては、ヘテロ原子として窒素原子、酸素原子及び/又は硫黄原子を1～3個有する5～14員の単環又は縮合環の基が好ましく、例えばピリジル基、ピリダジニル基、フリル基、チエニル基、インドリル基、チアゾリル基、イミダゾリル基、ベンゾフリル基、ベンゾチエニル基、ピロリジニル基、ピペリジニル基、モルホリニル基、ピペラジニル基が挙げられる。また、当該複素環式基に置換し得る基としては、ハロゲン原子、ヒドロキシル基、アルコキシ基、アシル基、保護されていてもよいアミノ基等が挙げられる。これらの置換基の具体例としては前記 $R^1$ 、 $R^2$  及び $R^3$  の炭化水素基の置換基と同様のものが挙げられる。

【0024】 $R^6$  で示されるアルコキシカルボニル基としては、炭素数1～12のアルコキシカルボニル基が挙げられ、その具体例としてはメトキシカルボニル基、エトキシカルボニル基、イソプロポキシカルボニル基、ブトキシカルボニル基等が挙げられる。

【0025】これらのメルカプトプロピオンアミド誘導体は、例えば特開昭57-24354号公報に記載の方法によって製造することができる。なお、これらのメルカプトプロピオン酸誘導体に哺乳類コラゲナーゼ抑制作用があることが知られているが、金属依存型エラスチン分解酵素阻害作用があることは全く知られていない。

【0026】また前記ホスホン酸誘導体及びメルカプトプロピオンアミド誘導体は、薬学的に許容される塩や水和物の形態で用いてもよい。

【0027】本発明のしわ形成予防剤は、皮膚の老化によるしわの発生に対して予防又は改善作用を有する。

【0028】本発明しわ形成予防剤の投与形態としては皮膚外用剤、経口剤などが挙げられるが、皮膚外用剤とするのが好ましい。皮膚外用剤とする場合の金属依存型エラスチン分解酵素阻害剤の配合量は、特に制限されな

いが、全組成に対し0.00001~10重量%、特に0.0001~5重量%とするのが好ましい。

【0029】本発明のしわ形成予防剤には、金属依存型エラスチン分解酵素阻害剤以外に紫外線吸収剤、紫外線防曇剤、コラーゲン、保湿剤、抗炎症剤、抗酸化剤等の成分を配合することができるが、特に紫外線吸収剤及び/又は紫外線防曇剤を配合するのが好ましい。

【0030】ここで、紫外線吸収剤としては、p-メトキシベンズ酸2-エチルヘキシル等が挙げられる。紫外線防曇剤としては、酸化チタン、酸化亜鉛等が挙げられる。保湿剤としては、ヒアルロン酸、セラミド類等が挙げられる。また抗炎症剤としては、アラントイン、グリチルリチン等が挙げられる。

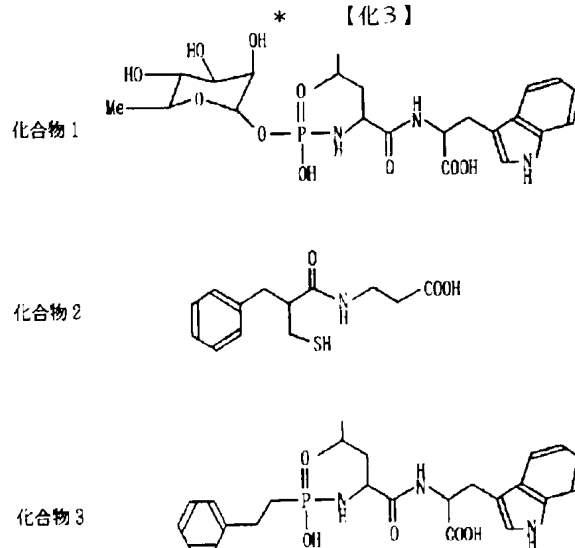
【0031】これらの紫外線吸収剤、紫外線防曇剤、コラーゲン、保湿剤、抗炎症剤、抗酸化剤等は、本発明のしわ形成予防剤中に0.001~99重量%、特に0.001~50重量%配合するのが好ましい。

【0032】本発明のしわ形成予防剤の具体的な剤型としては、クリーム、軟膏、ゲル、ローション、溶液、パック、ファンデーション等が挙げられ、これらの剤型とするにあたって各種油剤、界面活性剤、ゲル化剤、防腐剤、酸化防止剤、溶剤、アルコール、キレート剤、増粘剤、色素、香料、水等を配合することができる。

【0033】

【実施例】次に実施例を挙げて本発明をさらに詳細に説明するが、本発明はこれに限定されるものではない。

【0034】実施例1 培養ヒト線維芽細胞のエラスターゼ活性抑制試験



化合物4 エラスチナール

【0037】表1から明らかなように好中球由来のセリンプロテアーゼ型エラスターゼ阻害剤として知られている化合物4は、金属依存型エラスターゼであるヒト線維芽細胞由来の酵素に対しては抑制作用を示さなかった。※50

\*大日本製薬社より市販されている正常ヒト線維芽細胞は10%牛胎児血清を含むDME培地で継代培養し、本試験に供した。ラバーポリスマンを用いてシャーレからはがした細胞は、生理食塩水中に浮遊させ、低速の遠心分離器を使って細胞を集め、生理食塩水で、3回洗浄した。細胞は0.1% トリトン X-100/0.2M トリス-塩酸緩衝液(pH8.0)に浮遊させ、超音波破碎し、酵素液とした。酵素活性測定に基質には125 nM N-スクシニル-Ala-Ala-Ala-p-ニトロアニリドを用い、酵素液+サンプル100μlに1μl添加し、37℃で1時間反応させ、5μlの酢酸を加えて反応を停止させた。生成したニトロアニリン量は分光光度計で、405nmにおける吸光度を測定し、求めた。サンプル濃度を変えて、酵素活性抑制率をプロットし、50%抑制濃度(IC<sub>50</sub>)を求めた。結果を表1に示す。

【0035】

【表1】

| 化合物 | エラスターゼ阻害活性<br>IC <sub>50</sub> (μM) |
|-----|-------------------------------------|
| 1   | 0.019                               |
| 2   | 0.042                               |
| 3   | 0.050                               |
| 4   | 100μM で2.9%阻害                       |

【0036】

【化3】

※これに対し、化合物1、2及び3は金属依存型エラスターゼを強力に抑制した。

【0038】実施例2 ヘアレスマウスによるしわ形成抑制試験

ヘアレスマウス(HR、ICR、実験開始時6週齢)の背部に、健康線用ランプ(東芝製、SE20)で、1回の照射量が1MED以下となるように調節してUV-B光の照射を行い、直後にサンプルを含む80%エタノール溶液を100 $\mu$ lを塗布した。この作業を20週間にわたって行った。照射エネルギー量はUV Radiometer(TOKYO OPTICAL社製、UVR-305、365D)を用いて測定した。また、コントロールとして80%エタノールのみを塗布したものをサンプルと同様に試験した。試験終了後、形成されたしわの10度数を肉眼により下記の基準(しわ指数)で評価した。結果を表2に示す。

【0039】<しわ指数>

- 0:しわが無形成  
1:しわがかすかに形成  
2:しわが微量形成  
3:しわが若干形成  
4:しわが強固に形成

【0040】

#### 実施例3 クリーム

| (成分)          | (重量%) |
|---------------|-------|
| 化合物1          | 2     |
| スクワラン         | 5     |
| ステアリン酸        | 2     |
| グリセリンモノステアレート | 10    |
| エタノール         | 2     |
| パラオキシ安息香酸メチル  | 0.2   |
| セタノール         | 2     |
| オリーブ油         | 4     |
| ワセリン          | 5     |
| グリチルリチン酸      | 1     |
| ビタミンE         | 0.5   |
| セラミド          | 5     |
| 香料            | 微量    |
| 色素            | 微量    |
| 精製水           | 残量    |
| 計             | 100.0 |

【0044】

#### 実施例4 スキンローション

| (成分)          | (重量%) |
|---------------|-------|
| 化合物2          | 1     |
| グリセリンモノステアレート | 1     |
| エタノール         | 15    |
| ワロビレングリコール    | 4     |
| イソプロピルパルミテート  | 3     |
| ラノリン          | 1     |
| パラオキシ安息香酸メチル  | 0.1   |
| セラミド          | 1     |
| 香料            | 微量    |
| 色素            | 微量    |

\*【表2】

|        | 塗布濃度  | スコア             |
|--------|-------|-----------------|
| コントロール | -     | 3.06 $\pm$ 0.12 |
| 化合物1   | 1mM   | 1.30 $\pm$ 0.15 |
| 化合物2   | 1mM   | 2.69 $\pm$ 0.08 |
| 化合物3   | 10mM  | 1.75 $\pm$ 0.05 |
| 化合物4   | 100mM | 3.05 $\pm$ 0.10 |

【0041】表2から明らかなように、セリンプロテアーゼに属するエラスターゼ阻害剤はしわ形成抑制作用を示さなかったが、金属プロテアーゼに属するエラスターゼ阻害剤は優れたしわ形成抑制作用を示した。

【0042】次に、金属依存型エラスチン分解酵素阻害剤を配合した、しわ形成抑制用の外用剤の処方例を示す。

【0043】

| Q   | 10    |
|-----|-------|
| 精製水 | 残量    |
| 計   | 100.0 |

【0045】

|            |      |       |
|------------|------|-------|
| 実施例4       | バック剤 |       |
| (成分)       |      | (重量%) |
| 化合物3       |      | 3     |
| ポリビニルアルコール |      | 20    |
| グリセリン      |      | 5     |
| エタノール      |      | 16    |
| 香料         |      | 微量    |
| 色素         |      | 微量    |
| 精製水        |      | 残量    |
| 計          |      | 100.0 |

【0046】

|            |          |       |
|------------|----------|-------|
| 実施例5       | ファンデーション |       |
| (成分)       |          | (重量%) |
| 化合物1       |          | 1     |
| 球状シリカビース   |          | 20    |
| シリカ被覆セリサイト |          | 45    |
| 超微粒子酸化チタン  |          | 10    |
| 黄酸化鉄       |          | 3     |
| タルク        |          | 5     |
| マイカ        |          | 5     |
| ベンガラ       |          | 1     |
| グンジョウ      |          | 1     |
| バラベン       |          | 0.2   |
| 流動パラフィン    |          | 4.8   |
| スクワラン      |          | 4     |
| 計          |          | 100.0 |

【0047】

30\*わの形成を防止又は改善することができる。

【発明の効果】本発明によれば、皮膚の老化に伴なうし\*

フロントページの続き

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社研究所内

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CLAIMS

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[Claim(s)]

[Claim 1] The wrinkling formation preventive which makes an active principle the inhibitor to a metal-dependent elastin dialytic ferment.

[Claim 2] The wrinkling formation preventive according to claim 1 whose metal-dependent elastin dialytic ferment is an elastin dialytic ferment of the dermis fibroblast origin

[Claim 3] The wrinkling formation preventive according to claim 1 or 2 whose medication gestalt is a skin medicine for external application.

[Claim 4] Furthermore, the wrinkling formation preventive of the claim 1-3 which is a thing containing an ultraviolet ray absorbent or an ultraviolet-rays defense agent given in any one term.

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## DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[The technical field to which invention belongs] this invention relates to the wrinkling formation preventive which can prevent or improve occurrence of the wrinkling produced by aging of the skin still in detail about a wrinkling formation preventive.

[0002]

[Description of the Prior Art] As an example of representation of appearance change produced when the skin ages, there are a wrinkling, occurrence of sag, a decrement of a beam, a pigmentation, color tone change, etc. Among these, about the pigmentation, a research progresses, and various kinds of whitening agents are developed and marketed.

[0003] By the way, the present condition is being unable to say that the research is fully progressing about occurrence of a wrinkling. For example, although the charge of makeup which blended the collagen is used, sufficient wrinkling formation prevention effect is not acquired.

[0004] About occurrence of a wrinkling, especially relevance with ultraviolet rays is strengthened, calls optical aging aging of the skin produced by the UV irradiation, and is studied variously. However, the present condition is that the charge of makeup still replaced with an ultraviolet ray absorbent or an ultraviolet-rays defense agent is not developed.

[0005]

[Problem(s) to be Solved by the Invention] Therefore, the purpose of this invention is to offer the medicine or the charge of makeup which can prevent or improve formation of a wrinkling.

[0006]

[Means for Solving the Problem] then, [ which the elastin of a dermis increases by notably by aging of the skin, especially optical aging conventionally the place which this invention persons have examined variously paying attention to the relation of formation and the elastin of a wrinkling -- for example J Inrest.Dermatol. and 82-587-590 (1984), said -- since it is called 91:158-161 (1988) and this 103:182-186(1994)], it has been considered to lead to prevention of a wrinkling to decrease an elastin. On the other hand, as an elastin dialytic ferment, the thing of the neutrophil-leucocyte origin is usually used, and the prevention effect over formation of a wrinkling did not accept at all in the experiment using the inhibitor to the elastin dialytic ferment of this neutrophil-leucocyte origin. Then, although the thing belonging to a serine protease and the thing belonging to a metal-dependent protease were in the elastin dialytic ferment as a result of continuing a research further, only when the inhibitor to a metal-dependent elastin dialytic ferment is prescribed for the patient, it finds out that occurrence of a wrinkling can prevent intentionally, and came to complete this invention.

[0007] That is, this invention offers the wrinkling formation preventive which makes an active principle the inhibitor to a metal-dependent elastin dialytic ferment.

[0008]

[Embodiments of the Invention] As a metal-dependent elastin dialytic ferment inhibitor used for this invention, a metal-dependent elastase inhibitor, especially the metal-dependent elastase inhibitor of the dermis fibroblast origin are desirable. As such an inhibitor, it is 0.1% triton from the incubation Homo-sapiens fibroblast, for example, X-100/0.2M. The matter in which 50% or more of prevention activity is shown by 1mM in the enzyme activity system of measurement which made N-\*\*\*\*\*-Ala-Ala-Ala-p-nitroanilide the substrate is mentioned.

[0009] As an example of such a metal-dependent elastin dialytic ferment inhibitor, a \*\*\*\*\* acid derivative, a mercapto propione amide derivative, etc. are mentioned, for example.

[0010] As a \*\*\*\*\* acid derivative, it is the following general formula (1).

[0011]

[Formula 1]



[0012] The compound expressed with (R1, R2, and R3 show among a formula the sugar residue which may have the hydrocarbon group which may have the hydrogen atom and the substituent, or the substituent) is mentioned.

[0013] The inside of the above-mentioned formula (1), and R1 and R2 And R3 As a hydrocarbon group which may have the substituent shown, any of a saturated hydrocarbon machine, and an unsaturation hydrocarbon group are sufficient, and an alkyl group, alkenyl machine, alkynyl group, annular aryl group, and annular alkenyl machine, an aromatic hydrocarbon machine, an aralkyl machine, etc. are mentioned.



The thing of 1-24, especially the thing of a carbon number of 1-18 are [ these hydrocarbon groups ] desirable

[0014] An alkyl group, an annular alkyl group, and aromatic-hydrocarbon machine or an aralkyl machine is desirable among the aforementioned hydrocarbon groups. Here, as an alkyl group, the alkyl group of the carbon numbers 1-12 of the shape of a straight chain and the letter of branching is desirable, for example, a methyl group, an ethyl group, n-propyl group, an isopropyl machine, n-butyl, an isobutyl machine, sec-butyl, tert-butyl, n-pentyl machine, an isoamyl machine, tert-amyl group, n-hexyl machine, n-octyl machine, n-decyl group, n-dodecyl, etc. are mentioned. As an annular alkyl group, the alixele-like alkyl group of 5 - 7 member ring is desirable, and a cyclopentyl group, a cyclohexyl machine, a cycloheptyl machine, etc. are mentioned. As an aromatic-hydrocarbon machine, the aromatic-hydrocarbon machine of the carbon numbers 6-14, such as a phenyl group and a naphthyl group, is desirable. As an aralkyl machine, the alkyl group of the carbon numbers 1-5 replaced with the aromatic-hydrocarbon machine of carbon numbers 6-12 is desirable, for example, a phenyl methyl (= benzyl) machine, 1-phenylethyl (= phenethyl) machine, 1-naphthyl methyl group, 2-naphthyl methyl group, 2-(1-naphthyl) ethyl group, 2-(2-naphthyl) ethyl group, 3-phenylpropyl machine, etc. are mentioned.

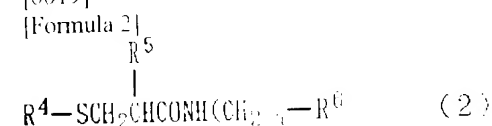
[0015] Moreover, as base which can be replaced by these hydrocarbon groups, a halogen atom, a hydroxyl, an alkoxy group, an acyl group, the amino group that may be protected, a heterocycle formula machine, etc. are mentioned. As a halogen atom, a chlorine atom, a bromine atom, an iodine atom, etc. are mentioned here. As an alkoxy group, the alkoxy group of carbon numbers 1-12 is desirable, for example, a methoxy machine, the ethoxy base, an isopropoxy group, etc. are mentioned. As an acyl group, the \*\*\*\*\* noil machine of carbon numbers 1-12 is desirable, for example, an acetyl group, a propionyl machine, the butyryl, etc. are mentioned. As an amino group which may be protected, the amino group, the acylamino machine, an alkylamino machine, a dialkylamino machine, etc. are mentioned. As a heterocycle formula machine, as a hetero atom, the base of the monocycle of 5 which has a nitrogen atom, an oxygen atom, and/or 1-3 sulfur atoms, - 14 members, or the condensed ring is desirable, for example, a pyridyl machine, a pilus \*\*\*\*\* machine, a furil machine, a thienyl group, an indolyl machine, a thiazolyl machine, an imidazolyl machine, a benzo furil machine, a benzo thienyl group, etc. are mentioned.

[0016] A monosaccharide residue, or an oligosaccharide residue is mentioned as a sugar residue. Moreover, as base which can be replaced by these sugar residue, an alkyl group, an acyl group, an aralkyl machine, etc. are mentioned. The thing same as an alkyl group, an acyl group, and an aralkyl machine as the above is mentioned here.

[0017] These \*\*\*\*\* acid derivatives can be manufactured by technique given in JP.5-105698.A.

[0018] As a mercapto propione amide derivative, it is the following general formula (2), for example.

[0019]



[0020] The compound expressed with (R4 shows a hydrogen atom or an acyl group among a formula, R5 shows the hydrocarbon group which may have the hydrogen atom or the substituent, R6 shows the heterocycle formula machine or acyl group which may have a hydrogen atom, the carboxyl group, the alkoxy carbonyl group, the hydrocarbon group that may have the substituent, and the substituent, and n shows the number of 1-20) is mentioned.

[0021] The inside of the above-mentioned formula (2), and R4 And R6 As an acyl group shown, a \*\*\*\*\* noil machine and an aryl carbonyl group are mentioned. As the concerned \*\*\*\*\* noil machine, the \*\*\*\*\* noil machine of carbon numbers 1-12 is desirable, for example, an acetyl group, a propionyl machine, a butyryl machine, etc. are mentioned. Moreover, as an aryl carbonyl group, the aryl carbonyl group of carbon numbers 7-15 is desirable, for example, a benzoyl, a substitute benzoyl, a naphthyl carbonyl group, a substitute naphthyl carbonyl group, etc. are mentioned. As base replaced by the benzoyl or the naphthyl carbonyl group here, an alkyl group, an alkoxy group, a halogen machine, the amino group, a hydroxy group, an alkanoloxo machine, etc. are mentioned.

[0022] R5 And R6 It is, even if it has the substituent shown, and as a hydrocarbon group, they are the above R1 and R2. And R3 The same thing is mentioned.

[0023] R6 As a heterocycle formula machine shown, as a hetero atom, the base of the monocycle of 5 which has a nitrogen atom, an oxygen atom, and/or 1-3 sulfur atoms, - 14 members, or the condensed ring is desirable, for example, a pyridyl machine, a pilus \*\*\*\*\* machine, a furil acid, a thienyl group, an indolyl machine, a thiazolyl machine, an imidazolyl machine, a benzo furil machine, a benzo thienyl group, a pyrrolidinyl machine, a piperidinyl machine, a mor \*\*\*\*\* machine, and Moreover, as base which can be replaced by the concerned heterocycle formula machine, a halogen atom, a hydroxyl, an alkoxy group, an acyl group, the amino group that may be protected are mentioned. As an example of these substituents, they are the above R1 and R2. And R3 The same thing as the substituent of a hydrocarbon group is mentioned.

[0024] R6 As an alkoxy carbonyl group shown, the alkoxy carbonyl group of carbon numbers 1-12 is mentioned, and a methoxycarbonyl group, an ethoxycarbonyl machine, an isopropoxy carbonyl group, a butoxy carbonyl group, etc. are mentioned as the example.

[0025] These mercapto propione amide derivatives can be manufactured by technique given in JP.57-24354.A. In addition, although it is known that mammal collagenase depressant action is in these mercapto propione amide derivatives, it is not known at all that there is metal-dependent elastinolytic ferment inhibitory action.

[0026] Moreover, you may use the aforementioned \*\*\*\*\* acid derivative and a mercapto propione amide derivative with the gestalt of the salt permitted pharmaceutically or a hydrate.

[0027] The wrinkling prevention, preventive of this invention has a prevention or an improvement operation to occurrence of the wrinkling by aging of the skin.

[0028] Although a skin medicine for external application, an oral agent, etc. are mentioned as medication gestalt of this invention wrinkling formation preventive, it is desirable to consider as a skin medicine for external application. Although especially the loadings of the metal-dependent elastinolytic ferment inhibitor in the case of considering as a skin medicine for external application are not restricted, it is desirable to consider [ as composed to ] total composition / especially [ as 0.0001 - 5 % of the weight 0.00001 to 10 % of the weight

[0029] Although components, such as an ultraviolet ray absorbent, an ultraviolet-rays defense agent, a collagen, a \*\*\*\* agent, an

anti-inflammatory agent and an anti-oxidant, can be blended with this invention wrinkling formation preventive in addition to a metal-dependent elastinolytic ferment inhibitor. It is desirable to blend an ultraviolet ray absorbent and/or an ultraviolet-rays defense agent especially.

[0030] Here, p-methoxy cinnamic acid 2-ethylhexyl etc. is mentioned as an ultraviolet ray absorbent. Titanium oxide, a zinc oxide, etc. are mentioned as an ultraviolet-rays defense agent. A hyaluronic acid and ceramides are mentioned as a \*\*\*\* agent. Moreover, an allantoin, glycyrrhizin, etc. are mentioned as an anti-inflammatory agent.

[0031] As for these ultraviolet ray absorbents, an ultraviolet-rays defense agent, a collagen, a \*\*\*\* agent, an anti-inflammatory agent, especially an anti-oxidant, etc., it is desirable to blend 0.001 to 50% of the weight 0.001 to 99% of the weight into the wrinkling formation preventive of this invention.

[0032] As a concrete pharmaceutical form of the wrinkling formation preventive of this invention, various oily medicines, a surfactant, a gelling agent, antiseptics, an antioxidant, a solvent, alcohol, a chelating agent, a thickener, coloring matter, perfume, water, etc. can be blended in mentioning a cream, the salve, gel, a lotion, a solution, a pack, foundation, etc., and considering as these pharmaceutical forms.

[0033]

[Example] Next, although an example is given and this invention is explained still in detail, this invention is not limited to this.

[0034] Example 1 The subculture of the normal Homo-sapiens fibroblast marketed from elastase activity suppression examination Dainippon Pharmaceutical Co., Ltd. of the incubation Homo-sapiens fibroblast was carried out by DMEM culture medium which contains fetal calf serum 10%, and the exam was presented with it. The cell stripped from the laboratory dish using the rubber policeman was made to float in a physiological saline. Collected cells using the low-speed centrifugal separation machine, is a physiological saline and washed them 3 times. A cell is 0.1% Triton X-100 (0.2M The tris-hydrochloric-acid buffer solution (pH8.0) was made to float, ultrasomic spallation was carried out, and it considered as enzyme liquid. In the substrate of enzyme activity measurement, they are 125mMs. Carried out 1microl addition, it was made to start to enzyme liquid + sample 100microl at 37 degrees C for 1 hour using N-succinyl-Ala-Ala-Ala-p-nitroanilide, the acetic acid of 5microl was added, and the reaction was stopped. The generated amount of nitroanilines is a spectrophotometer, and measured and asked for the absorbance in 405nm. Sample concentration was changed, the rate of enzyme activity suppression was plotted, and it asked for suppression concentration (IC50) 50%. A result is shown in Table 1.

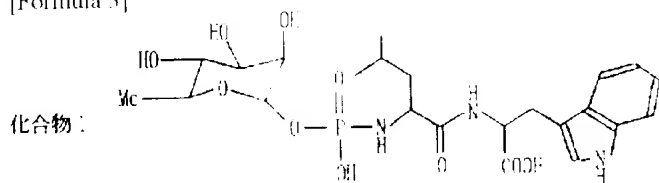
[0035]

[Table 1]

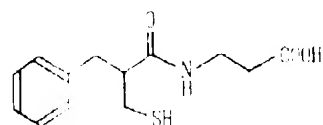
| 化合物 | エラスターゼ阻害活性<br>IC <sub>50</sub> (μM) |
|-----|-------------------------------------|
| 1   | 0.019                               |
| 2   | 0.042                               |
| 3   | 0.050                               |
| 4   | 100 μM で 2.9 % 阻害                   |

[0036]

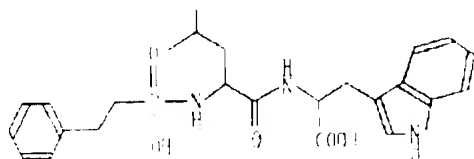
[Formula 3]



化合物 2



化合物 3



化合物 4

エラスターゼ

[0037] The compound 4 is shown as a serine-protease type elastase inhibitor of the neutrophil-leucocyte origin so that clearly from Table 1 did not show depressant action to the enzyme of the Homo-sapiens fibroblast origin which is a metal-dependent elastase. On the other hand,

compounds 1, 2, and 3 expressed the metal-dependent elastase powerfully

[0038] Example 2 With the lamp for healthy lines (the Toshiba make, SE20), it adjusted so that 1 time of an exposure might be set to 1 or less MED, and UV-B light was irradiated, and 10mmol/l was applied behind the wrinkling formation suppression examination hair loss mouse (HR/ICR, time of experiment start 6 week-old) by the hair loss mouse for 80% ethanol solution which contains a sample immediately after. This work was performed over 20 weeks. The amount of irradiation energy was measured using UV-Radiometer (the product made from TOKYO DENSHI KAGAKU, UVR-3 (S-3651D)). Moreover, what applied only ethanol 80% as control was examined like the sample. The naked eye estimated the frequency of the formed wrinkling on the following criteria (wrinkling exponent) after the examination end. A result is shown in Table 2.

[0039] For a minute amount formation 3 wrinkling, a some formation 4 wrinkling is | a <wrinkling exponent> 0 wrinkling / an aplasia 1 wrinkling / a formation 2 wrinkling | formation [0040] firmly faintly.

[Table 2]

|        | 塗布濃度  | スコア         |
|--------|-------|-------------|
| コントロール | -     | 3.00 ± 0.12 |
| 化合物 1  | 10μM  | 2.30 ± 0.15 |
| 化合物 2  | 10μM  | 2.66 ± 0.08 |
| 化合物 3  | 10μM  | 1.75 ± 0.05 |
| 化合物 4  | 100μM | 3.05 ± 0.10 |

[0041] Although the elastase inhibitor belonging to a serine protease did not show wrinkling formation depressant action so that clearly from Table 2, the elastase inhibitor belonging to a metal protease showed the outstanding wrinkling formation depressant action.

[0042] Next, the example of prescription of the medicine for external application for wrinkling formation suppression which blended the metal-dependent elastinolytic ferment inhibitor is shown.

[0043]

Example 3 Cream (component) (weight %)

A compound 1 2 Squalane 5 Stearin acid 2 Glycerol monostearate 10 Ethanol 2 Methyl parahydroxybenzoate 0.2 Cetanol 2 Olive oil 4 Vaseline 5 Glycyrrhizic acid 1 Vitamin E 0.5 Ceramide 5 Perfume Minute amount Coloring matter Minute amount Purified water Residue Total 100.0 [0044]

Example 4 Skin lotion (component) (weight %)

A compound 2 1 Glycerol monostearate 1 Ethanol 15 Propylene glycol 4 Isopropyl palmitate 3 Lanolin 1 Methyl parahydroxybenzoate 0.1 Ceramide 1 Perfume Minute amount Coloring matter Minute amount Purified water Residue Total 100.0 [0045]

Example 4 Pack agent (component) (weight %)

A compound 3 3 Polyvinyl alcohol 20 Glycerol 5 Ethanol 16 Perfume Minute amount Coloring matter Minute amount Purified water Residue Total 100.0 [0046]

Example 5 Foundation (component) (weight %)

A compound 1 1 Spherical silica \*\*\*\*\* 20 Silica covering sericite 45 Ultrafine particle titanium oxide 10 Yellow iron oxide 3 Tale 5 Mica 5 Red ocher 1 Ultramarine 7 Paraben 0.2 Liquid paraffin 4.8 Squalane 4 Total 100.0 [0047]

[Effect of the Invention] According to this invention, formation of the wrinkling accompanied by aging of the skin can be prevented or improved.

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Field

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[The technical field to which invention belongs] this invention relates to the wrinkling formation preventive which can prevent or improve occurrence of the wrinkle produced by aging of the skin still in detail about a wrinkling formation preventive.

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Technique

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[Description of the Prior Art] As an example of representation of appearance change produced when the skin ages, there are a wrinkling, occurrence of sag, a decrement of a beam, a pigmentation, color tone change, etc. Among these, about the pigmentation, a research progresses, and various kinds of whitening agents are developed and marketed.

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[0004] About occurrence of a wrinkling, especially relevance with ultraviolet rays is strengthened, calls optical aging aging of the skin produced by the UV irradiation, and is studied variously. However, the present condition is that the charge of makeup still replaced with an ultraviolet ray absorbent, an ultraviolet-rays defense agent is not developed.

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Effect

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[Effect of the Invention] According to this invention, formation of the wrinkling accompanied by aging of the skin can be prevented or improved.

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TECHNICAL PROBLEM

---

[Problem(s) to be Solved in the Invention] Therefore, the purpose of this invention is to offer the medicine or the charge of makeup which can prevent or improve formation of a wrinkling

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MEANS

[Means for Solving the Problem] then, [ which the elastin of a dermis increases by notably by aging of the skin, especially optical aging conventionally the place which this invention persons have examined variously paying attention to the relation of formation and the elastin of a wrinkling -- for example, J. Invest Dermatol. and 82,587-590 (1984), said -- since it is called 91:158-161 (1988) and this 103,182-186(1994)], it has been considered to lead to prevention of a wrinkling to decrease an elastin. On the other hand, as an elastin dialytic ferment, the thing of the neutrophil-leucocyte origin is usually used, and the prevention effect over formation of a wrinkling did not accept at all in the experiment using the inhibitor to the elastin dialytic ferment of this neutrophil-leucocyte origin. Then, although the thing belonging to a serine protease and the thing belonging to a metal-dependent protease were in the elastin dialytic ferment as a result of continuing a research further, only when the inhibitor to a metal-dependent elastin dialytic ferment is prescribed for the patient, it finds out that occurrence of a wrinkling can prevent intentionally, and came to complete this invention.

[0007] That is, this invention offers the wrinkling formation preventive which makes an active principle the inhibitor to a metal-dependent elastin dialytic ferment

[0008]

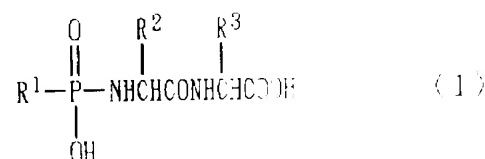
[Embodiments of the Invention] As a metal-dependent elastin dialytic ferment inhibitor used for this invention, a metal-dependent elastase inhibitor, especially the metal-dependent elastase inhibitor of the dermis fibroblast origin are desirable. As such an inhibitor, it is 0.1% triton from the incubation Homo-sapiens fibroblast, for example, X-100/0.2M. The matter in which 50% or more of prevention activity is shown by 1mM in the enzyme activity system of measurement which made N-\*\*\*\*\*-Ala-Ala-p-nitroanilide the substrate is mentioned using the enzyme liquid contacted with the tris-hydrochloric-acid buffer solution (pH 8.0).

[0009] As an example of such a metal-dependent elastin dialytic ferment inhibitor, a \*\*\*\*\* acid derivative, a mercapto propione amide derivative, etc. are mentioned, for example.

[0010] As a \*\*\*\*\* acid derivative, it is the following general formula (1).

[0011]

[Formula 1]



[0012] The compound expressed with (R1, R2, and R3 show among a formula the sugar residue which may have the hydrocarbon group which may have the hydrogen atom; and the substituent, or the substituent) is mentioned.

[0013] The inside of the above-mentioned formula (1), and R1 and R2 And R3 As a hydrocarbon group which may have the substituent shown, any of a saturated hydrocarbon machine and an unsaturation hydrocarbon group are sufficient, and an alkyl group, alkenyl machine, alkynyl group, annular alkyl group, and annular alkenyl machine, an aromatic-hydrocarbon machine, an aralkyl machine, etc. are mentioned. The thing of 1-24, especially, the thing of a carbon number of 1-18 are [ these hydrocarbon groups ] desirable.

[0014] An alkyl group, an annular alkyl group, and aromatic-hydrocarbon machine or an aralkyl machine is desirable among the aforementioned hydrocarbon groups. Here, as an alkyl group, the alkyl group of the carbon numbers 1-12 of the shape of a straight chain and the letter of branching is desirable, for example, a methyl group, an ethyl group, n-propyl group, an isopropyl machine, n-butyl, an isobutyl machine, sec-butyl, tert-butyl, n-pentyl machine, an isoamyl machine, tert-amyl group, n-hexyl machine, n-octyl machine, n-decyl group, n-dodecyl, etc. are mentioned. As an annular alkyl group, the alicyclic-like alkyl group of 5 - 7 member ring is desirable, and a cyclopentyl group, a cyclohexyl machine, a cycloheptyl machine, etc. are mentioned. As an aromatic-hydrocarbon machine, the aromatic-hydrocarbon machine of the carbon numbers 6-14, such as a phenyl group and a naphthyl group, is desirable. As an aralkyl machine, the alkyl group of the carbon numbers 1-5 replaced with the aromatic-hydrocarbon machine of carbon numbers 6-12 is desirable, for example, a phenyl methyl (= benzyl) machine, 2-phenylmethyl (= phenethyl) machine, 1-naphthyl methyl group, 2-naphthyl methyl group, 2-(1-naphthyl) ethyl group, 2-(2-naphthyl) ethyl group, 3-phenylpropyl machine, etc. are mentioned.

[0015] Moreover, as bases which can be replaced by these hydrocarbon groups, a halogen atom, a hydroxyl, an alkoxy group, an acyl group, the amino group that may be protected, a heterocycle formula machine, etc. are mentioned. As a halogen atom, a chlorine atom, a bromine atom, an iodine atom, etc. are mentioned here. As an alkoxy group, the alkoxy group of carbon numbers 1-12 is desirable, for example, a methoxy machine, the ethoxy base, an isopropoxy group, etc. are mentioned. As an acyl group, the \*\*\*\*\* noil machine of carbon numbers 1-12 is desirable, for example, an acetyl group, a propionyl machine, the butyryl, etc. are mentioned. As an amino group which may be protected, the amino group, the cyclamino machine, an alkylamino machine, a dialkylamino machine, etc. are mentioned. As a heterocycle



formula machine, as a hetero atom, the base of the monocycle of 5 which has a nitrogen atom, an oxygen atom, and/or 1-3 sulfur atoms, - 14 members, or the condensed ring is desirable, for example, a pyridyl machine, a pilus \*\*\*\*\* machine, a furil machine, a thienyl group, an indolyl machine, a thiazolyl machine, an imidazolyl machine, a benzo furil machine, a benzo thienyl group, etc. are mentioned.

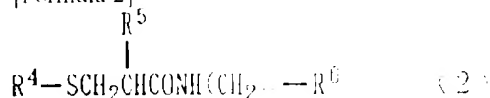
[0016] A monosaccharide residue or an oligosaccharide residue is mentioned as a sugar residue. Moreover, as base which can be replaced by these sugar residues, an alkyl group, an acyl group, an aralkyl machine, etc. are mentioned. The thing same as an alkyl group, an acyl group, and an aralkyl machine as the above is mentioned here.

[0017] These \*\*\*\*\* acid derivatives can be manufactured by technique given in JP.5-105698.A.

[0018] As a mercaptopropione amide derivative, it is the following general formula (2), for example.

[0019]

[Formula 2]



[0020] The compound expressed with (R<sup>4</sup>) shows a hydrogen atom or an acyl group among a formula, R<sup>5</sup> shows the hydrocarbon group which may have the hydrogen atom or the substituent, R<sup>6</sup> shows the heterocycle formula machine or acyl group which may have a hydrogen atom, the carboxyl group, the alkoxy carbonyl group, the hydrocarbon group that may have the substituent, and the substituent, and n shows the number of 1-20 is mentioned.

[0021] The inside of the above-mentioned formula (2), and R<sup>4</sup> And R<sup>6</sup> As an acyl group shown, a \*\*\*\*\* noil machine and an aryl carbonyl group are mentioned. As the concerned \*\*\*\*\* noil machine, the \*\*\*\*\* noil machine of carbon numbers 1-12 is desirable, for example, an acetyl group, a propionyl machine, a butyryl machine, etc. are mentioned. Moreover, as an aryl carbonyl group, the aryl carbonyl group of carbon numbers 7-15 is desirable, for example, a benzoyl, a substitute benzoyl, a naphthyl carbonyl group, a substitute naphthyl carbonyl group, etc. are mentioned. As base replaced by the benzoyl or the naphthyl carbonyl group here, an alkyl group, an alkoxy group, a halogen machine, the amino group, a hydroxy group, an alkanoloxyl machine, etc. are mentioned.

[0022] R<sup>5</sup> And R<sup>6</sup> It is, even if it has the substituent shown, and as a hydrocarbon group, they are the above R<sup>1</sup> and R<sup>2</sup>. And R<sup>3</sup> The same thing is mentioned.

[0023] R<sup>6</sup> As a heterocycle formula machine shown, as a hetero atom, the base of the monocycle of 5 which has a nitrogen atom, an oxygen atom, and/or 1-3 sulfur atoms, - 14 members, or the condensed ring is desirable, for example, a pyridyl machine, a pilus \*\*\*\*\* machine, a furil acid, a thienyl group, an indolyl machine, a thiazolyl machine, an imidazolyl machine, a benzo furil machine, a benzo thienyl group, a pyrrolidinyl machine, a piperidinyl machine, a mol \*\*\*\*\* machine, and Moreover, as base which can be replaced by the concerned heterocycle formula machine, a halogen atom, a hydroxyl, an alkoxy group, an acyl group, the amino group that may be protected are mentioned. As an example of these substituents, they are the above R<sup>1</sup> and R<sup>2</sup>. And R<sup>3</sup> The same thing as the substituent of a hydrocarbon group is mentioned.

[0024] R<sup>6</sup> As an alkoxy carbonyl group shown, the alkoxy carbonyl group of carbon numbers 1-12 is mentioned, and a methoxycarbonyl group, an ethoxycarbonyl machine, an isopropoxy carbonyl group, a butoxy carbonyl group, etc. are mentioned as the example.

[0025] These mercaptopropione amide derivatives can be manufactured by technique given in JP.57-24354.A. In addition, although it is known that mammal collagenase depressant action is in these mercaptopropionic acid derivatives, it is not known at all that there is metal-dependent elastinolytic ferment inhibitory action.

[0026] Moreover, you may use the aforementioned \*\*\*\*\* acid derivative and a mercapto propione amide derivative with the gestalt of the salt permitted pharmacologically or a hydrate.

[0027] The wrinkling formation preventive of this invention has a prevention or an improvement operation to occurrence of the wrinkling by aging of the skin.

[0028] Although a skin medicine for external application, an oral agent, etc. are mentioned as medication gestalt of this invention wrinkling formation preventive, it is desirable to consider as a skin medicine for external application. Although especially the loadings of the metal-dependent elastinolytic ferment inhibitor in the case of considering as a skin medicine for external application are not restricted, it is desirable to consider [as opposed to] total composition / especially [as 0.0001 - 5 % of the weight 0.00001 to 10% of the weight.

[0029] Although components, such as an ultraviolet ray absorbent, an ultraviolet-rays defense agent, a collagen, a \*\*\*\* agent, an anti-inflammatory agent, and an anti-oxidant, can be blended with this invention wrinkling formation preventive in addition to a metal-dependent elastinolytic ferment inhibitor, it is desirable to blend an ultraviolet ray absorbent and/or an ultraviolet-rays defense agent especially.

[0030] Here, p-methoxy cinnamic acid 2-ethylhexyl etc. is mentioned as an ultraviolet ray absorbent. Titanium oxide, a zinc oxide, etc. are mentioned as an ultraviolet-rays defense agent. A hyaluronate acid and ceramides are mentioned as a \*\*\*\* agent. Moreover, an allantoin, glycyrrhizin, etc. are mentioned as an anti-inflammatory agent.

[0031] As for these ultraviolet ray absorbents, an ultraviolet-rays defense agent, a collagen, a \*\*\*\* agent, an anti-inflammatory agent, especially an anti-oxidant, etc., it is desirable to blend 0.001 to 50% of the weight 0.001 to 99% of the weight into the wrinkling formation preventive of this invention.

[0032] As a concrete pharmaceutical form of the wrinkling formation preventive of this invention, various oily medicines, a surfactant, a gelling agent, antiseptics, an antioxidant, a solvent, alcohol, a chelating agent, a thickener, coloring matter, perfume, water, etc. can be blended in mentioning a cream, the salve, gel, a lotion, a solution, a pack, foundation, etc., and considering as these pharmaceutical forms.

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EXAMPLE

[Example] Next, although an example is given and this invention is explained still in detail, this invention is not limited to this.

[0034] Example 1 The subculture of the normal Homo-sapiens fibroblast marketed from elastase activity suppression examination Damippon Pharmaceutical Co., Ltd. of the incubation Homo-sapiens fibroblast was carried out by DMEM culture medium which contains fetal calf serum 10%, and the exam was presented with it. The cell stripped from the laboratory dish using the rubber policeman was made to float in a physiological saline, collected cells using the low-speed centrifugal separation machine, in a physiological saline and washed them 3 times. A cell is 0.1%, Triton X-100 (0.2M) The tris-hydrochloric-acid buffer solution (pH8.0) was made to float, ultrasonic spallation was carried out, and it considered as enzyme liquid. In the substrate of enzyme activity measurement, they are 125mMs. Carried out 1microl addition, it was made to react to enzyme liquid + sample 100microl at 37 degrees C for 1 hour using N-succinyl-Ala-Ala-Ala-p-nitroanilide, the acetic acid of 5microl was added, and the reaction was stopped. The generated amount of nitroanilines is a spectrophotometer, and measured and asked for the absorbance in 405nm. Sample concentration was changed, the rate of enzyme activity suppression was plotted, and it asked for suppression concentration (IC50) 50%. A result is shown in Table 1.

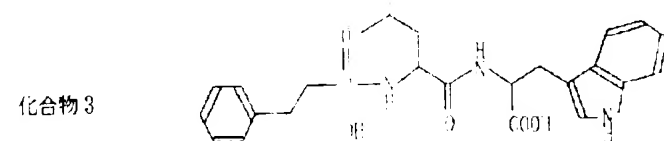
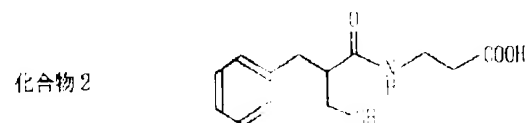
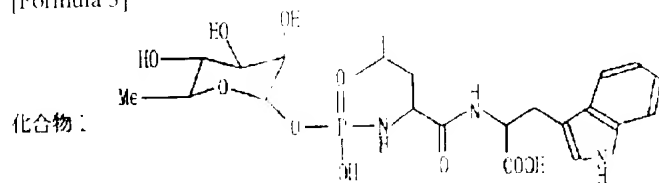
[0035]

[Table 1]

| 化合物 | エステラーゼ阻害活性<br>IC <sub>50</sub> (μM) |
|-----|-------------------------------------|
| 1   | 0.019                               |
| 2   | 0.042                               |
| 3   | 0.050                               |
| 4   | 100 μM で 2.9 % 阻害                   |

[0036]

[Formula 3]



化合物 4 エラスターール

[0037] The compound 4 shown as a serine-protease type elastase inhibitor of the neutrophil-leucocyte origin so that clearly from Table 1 did not show depressant action to the enzyme of the Homo-sapiens fibroblast origin which is a metal-dependent elastase. On the other hand, compounds 1, 2, and 3 suppressed the metal-dependent elastase powerfully.

[0038] Example 2 With the lamp for health lines (the Toshiba make, SF-20), it adjusted so that 1 time of an exposure may be set to 1 or less MED, and UV-B light was irradiated, and 100microl was applied behind the wrinkling formation suppression examination hair loess mouse (HR/ICR, time of experiment start 6 week-old) by the hair loess mouse for 80% ethanol solution which contains a sample immediately after. This work was performed over 20 weeks. The amount of irradiation energy was measured using UV radiometer (the product made from TOKYO DENSHI CO., LTD. UVF-305-365D). Moreover, what applied only ethanol 80% as control was examined like the sample. The naked eye estimated the frequency of the formed wrinkling on the following criteria (wrinkling exponent after the examination end). A result is shown in Table 2.

[0039] For a minute amount formation: 3 wrinkling, a some formation: 4 wrinkling is | a <wrinkling exponent < 0 wrinkling | an aplasia 1 wrinkling / a formation: 1 wrinkling / a formation [0040] firmly faintly

[Table 2]

|        | 塗布濃度  | ワ、コ、ウ       |
|--------|-------|-------------|
| コントロール | -     | 3.00 ± 0.12 |
| 化合物 1  | 1μM   | 2.30 ± 0.15 |
| 化合物 2  | 1μM   | 2.65 ± 0.05 |
| 化合物 3  | 10μM  | 2.75 ± 0.15 |
| 化合物 4  | 100μM | 3.05 ± 0.10 |

[0041] Although the elastase inhibitor belonging to a serine protease did not show wrinkling formation depressant action, so that clearly from Table 2, the elastase inhibitor belonging to a metal protease showed the outstanding wrinkling formation depressant action.

[0042] Next, the example of prescription of the medicine for external application for wrinkling formation suppression which blended the metal-dependent elastase catalytic ferment inhibitor is shown.

[0043]

Example 3 Cream (component weight %)

A compound 1: 2 Squalane 5 Stearic acid 2 Glycerol monostearate 10 Ethanol 2 Methyl parahydroxybenzoate 0.2 Cetanol 2 Olive oil 4 Vaseline 5 Glycyrrhizic acid 1 Vitamin E 0.5 Ceramide 5 Perfume Minute amount Coloring matter Minute amount Purified water Residue Total 100.0 [0044]

Example 4 Skin lotion (component weight %)

A compound 2: 1 Glycerol monostearate 1 Ethanol 15 Propylene glycol 4 Isopropyl palmitate 3 Lanolin 1 Methyl parahydroxybenzoate 0.1 Ceramide 1 Perfume Minute amount Coloring matter Minute amount Purified water Residue Total 100.0 [0045]

Example 4 Pack agent (component weight %)

A compound 3: 3 Polyvinyl alcohol 20 Glycerol 5 Ethanol 10 Perfume Minute amount Coloring matter Minute amount Purified water Residue Total 100.0 [0046]

Example 5 Foundation (component weight %)

A compound 1: 1 Spherical silica 2 Silica covering sericite 45 Ultrafine particle titanium oxide 10 Yellow iron oxide 3 Tale 5 Mica 5 Red ochre 1 Ultramarine 1 Parabens 2 Liquid paraffin 4.8 Squalane 4 Total 100.0

[Translation done.]

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Correction and a correction

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[Document to be Amended] Specification

[Item(s) to be Amended] Claim

[Method of Amendment] Change

[Proposed Amendment]

[Claim(s)]

[Claim 1] The wrinkling formation preventive which makes an active principle the inhibitor to a metal-dependent elastin dialytic ferment.

[Claim 2] The wrinkling formation preventive according to claim 1 whose metal-dependent elastin dialytic ferment is an elastin dialytic ferment of the dermis fibroblast origin.

[Claim 3] The inhibitor to a metal-dependent elastin dialytic ferment is 0.1% triton from the incubation Homo-sapiens fibroblast.

X-100/0.2M Wrinkling formation preventive according to claim 1 which is the matter in which 50% or more of prevention activity is shown by 1mM in the enzyme activity system of measurement which made N-\*\*\*\*\*-Ala-Ala-Ala-p-nitroanilide the substrate using the enzyme liquid extracted with the tris hydrochloric-acid buffer solution (pH 8.0)

[Claim 4] The wrinkling formation preventive of the claim 1-3 whose medication gestalt is a skin medicine for external application given in any one term

[Claim 5] Furthermore, the wrinkling formation preventive of the claim 1-4 which is a thing containing an ultraviolet ray absorbent or an ultraviolet-rays defense agent given in any one term

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[Translation done]